REMARKS

Claims 1-125 are pending. Claims 20-37 and 46-125 are withdrawn. Thus, claims 1-19 and 38-45 are under consideration. Claims 1-18 and 38 have been amended to recite isolated detoxified pneumococcal neuraminidases or antigenic fragments thereof. Support for this amendment can be found throughout the specification, for example, on page 50, lines 9-11.

Applicants respectfully acknowledge the rejoinder of claims 38-45 with claims 1-19 for examination.

35 U.S.C. § 112

The Examiner rejected claims 1-19 and 38-45 under 35 U.S.C. § 112 for allegedly failing to meet the written description requirement. Applicants respectfully traverse this rejection.

Claims 1-17 recite isolated detoxified pneumococcal neuraminidases or antigenic portions thereof. Claim 18 recites a composition comprising an isolated detoxified pneumococcal neuraminidase or an antigenic portion thereof and a pharmaceutically acceptable carrier. Claim 19 recites the composition of claim 18 further comprising an adjuvant. Claim 38 recites a composition comprising an isolated detoxified pneumococcal neuraminidase or an antigenic portion thereof and a pharmaceutically acceptable carrier, wherein the composition is suitable for administration to a mucosal surface. Claims 39-45 depend from claim 38, and, thus, include each and every limitation of claim 38.

The Examiner, at page 4, line 17, to page 5, line 3, of the Office Action, stated that, "[s]ince the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, 'detoxified pneumococcal neuraminidase' alone is insufficient to describe the genus. One of skill in the art would reasonably conclude the disclosure fails to provide a representative number of species to describe the genus." M.P.E.P. § 2163 states, "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." One of skill in the art would reasonably conclude that the applicant had possession of the claimed compounds. "An applicant may also show that an invention is complete by disclosure of

sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when couple with a known or disclosed correlation between function and structure, or some combination of such characteristics." See M.P.E.P. § 2163. "For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length." *Id.*

Applicants note detoxified pneumococcal neuraminidases or antigenic fragments thereof and methods of making detoxified pneumococcal neuraminidases or antigenic fragments thereof are described in the specification at pages 15-19. Pages 12-14 and Table 1 of the specification provide the sequences for several neuraminidases. The specification at page 15 describes how one of skill in the art can produce a detoxified pneumococcal neuraminidase. Specifically, the specification at page 15, lines 2-8, states, "[t]hus, the naturally occurring neuraminidase can be modified by substitution, deletion, or alteration of amino acid residues in accordance with the methods taught herein. Optionally, such modifications will be designed to detoxify the neuraminidase. ***By 'detoxification' is meant a reduction or elimination in enzymatic activity, while maintaining antigenicity or immunogenicity.*** This is accomplished by substitution, deletion, or alteration of amino acids in the active site of the neuraminidase using site specific mutagenesis." Further, the specification at page 15, line 31, to page 16, line 2, states, "[a]s described above, a detoxified neuraminidase is a neuraminidase that exhibits decreased activity as compared to non-detoxified neuraminidase as measured by the assay of Lock et al., (Microb. Pathog. 4:33-43, 1988), which is well known in the art." Further, the specific amino acids to be substituted, deleted, or altered are described throughout the specification at pages 15-19. Therefore, those of skill in the art would recognize that the Applicants had possession of the claimed isolated detoxified pneumococcal neuraminidases or antigenic fragments thereof as of the filing date.

The Examiner, at page 5, lines 6-8, of the Office Action, states, "[a]dequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating. The protein itself is required." Applicants note the sequences of several neuraminidases are provided on pages 13 and 14 in the specification. Additionally, as

stated above, the specification at pages 15-19 describes the amino acid sequences to be targeted to create a detoxified pneumococcal neuraminidase. Specifically, the specification at page 15, lines 12-13, states, "[s]uch substitutions, deletions, or alterations can also occur within the Asp boxes within amino acid residues 383-387, 467-473, 541-546, or 610-616." By way of another example, the specification at page 15, lines 24-27, states, "[a]lso provided are neuraminidases with modifications in the regions corresponding to amino acid residues 340-350, 600-610, or 360-370. More specifically, the arginines at positions 347, 605, 366, or 367 can be substituted with lysine or glutamine, or any other conservative or non-conservative amino acids." Further, multiple detoxified pneumococcal neuraminidases are described in Example 2 in the present application.

The Examiner, at page 6 of the Office Action, directs the Applicants to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. § 112, 1 "Written Description" Requirement, Example 10 asserting that the present case is similar to this Example. Example 10 is drawn to products claimed by its function. In the Example, claim 3 is directed to the genus of variants of SEQ ID NO:3 that comprise an amino acid sequence at least 95% identical to SEQ ID NO:3 and catalyzes the reaction A→B. This claim was deemed to fail to satisfy the written description requirement since one of skill in the art would not be able to identify without further testing which of those proteins having at least 95% identity to SEQ ID NO:3 (if any) have the activity of catalyzing the reaction A→B. However, this Example is not similar to the present application. As described above, the protein sequence of several neuraminidases are provided in the specification. Further, the specification provides the amino acid sequences to target to create a detoxified neuraminidase. Specifically, at page 15, lines 8-13, the specification states, "[p]referably, such substitutions, deletions, or alterations will be within the Asp boxes (i.e., within amino acid residues 460-480, 530-560, or 600-620)....Such substitutions, deletions, or alterations can also occur within the Asp boxes within amino acid residues 383-387, 467-473, 541-546, or 610-616." Other alterations are described in the specification at page 16, lines 16-31. Additionally, specific examples of detoxified pneumococcal neuraminidases are provided in Example 2, as stated above. Therefore, the present application has satisfied the written description requirement, as the present application has conveyed with reasonable clarity to those

of skill in the art that the Applicants, at the time of filing, were in possession of the claimed isolated detoxified pneumococcal neuraminidases or antigenic fragments thereof. As such, claims 1-19 and 38-45 comply with the written description requirement. Applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 102(b)

The Examiner rejected claims 1-5, 18-19, 38, and 42 under 35 U.S.C. § 102(b) for allegedly being anticipated by U.S. Patent No. 5,792,457 ("Tuomanen"). Applicants respectfully traverse this rejection for at least two reasons. First, heat killed bacteria do not necessarily contain a detoxified pneumococcal neuraminidase. The Examiner states, on page 7, that the heat killed pneumococcal R6 strain inherently contains detoxified pneumococcal neuraminidase enzymes. Applicants note, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is ***necessarily*** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. *The mere fact that a certain thing may result from a given set of circumstances is not sufficient.*'" *In re Robertson*, 49USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Tuomanen fails to disclose or suggest a detoxified pneumococcal neuraminidase and the extrinsic evidence does not clarify that the missing descriptive matter is ***necessarily*** present. Further, the mere probability or possibility of a detoxified pneumococcal neuraminidase being in the heat killed pneumococcal R6 strain is not sufficient for asserting that Tuomanen anticipates the detoxified pneumococcal neuraminidases of the present application. As such, claims 1-5 and 18-19 are novel. Applicants respectfully request reconsideration and withdrawal of this rejection.

Second, claims 1-5, 18, and 19, as amended, recite an isolated detoxified neuraminidase. The Examiner, at page 7, lines 1-7, of the Office Action, argues that Tuomanen discloses a heat killed pneumococcus strain that inherently contains detoxified pneumococcal neuraminidase enzymes. Applicants note, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). While

Tuomanen describes a heat killed pneumococcal R6 strain, Tuomanen fails to disclose or suggest an *isolated* detoxified neuraminidase or an antigenic portion thereof. Further, Tuomanen fails to disclose or suggest compositions comprising an isolated detoxified pneumococcal neuraminidase or an antigenic portion thereof. In contrast, the present application provides isolated detoxified pneumococcal neuraminidases at least at pages 15-19. As described in the application on page 15, line 31, to page 16, line 1, detoxified neuraminidases have decreased enzymatic activity as compared to non-detoxified neuraminidases. Such detoxified neuraminidases are not described or suggested by Tuomanen. As Tuomanen fails to disclose or suggest each and every element of the claims, Tuomanen fails to anticipate claims 1-5 and 18-19.

Further, Tuomanen fails to anticipate claims 38 and 42. Claim 38 recites a composition comprising an isolated detoxified pneumococcal neuraminidase or an antigenic portion thereof and a pharmaceutically acceptable carrier, wherein the composition is suitable for administration to a mucosal surface. Claim 42 recites a container comprising the composition of claim 38. Tuomanen describes injecting rabbits intracisternally with the heat killed pneumococcus R6 strain. See Example 10, 3rd paragraph. Tuomanen, thus, fails to disclose or suggest a composition comprising an isolated detoxified pneumococcal neuraminidase or an antigenic portion thereof and a pharmaceutically acceptable carrier, wherein the composition is suitable for administration to a mucosal surface. Additionally, Tuomanen fails to even consider administration to a mucosal surface. Tuomanen also fails to disclose or suggest a container comprising the composition that is suitable for administrating to a mucosal surface. Therefore, Tuomanen fails to disclose or suggest each and every element of the claims, and, thus, Tuomanen fails to anticipate claims 38 and 42. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner rejected claims 1-19, 38, and 42 under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 02/077021 ("Masignani"). Applicants respectfully traverse this rejection.

The Examiner stated that Masignani discloses pneumococcal neuraminidase fragments as small as 7 consecutive amino acid residues for vaccination purposes, and since the present

application defines "detoxified" as a reduction in enzymatic activity that is accomplished via substitutions, deletions, or alterations of amino amino acids in the active site of the neuraminidase, that Masignani anticipates the claims of the present application. As stated above, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 9Fed. Cir. 1987). While Masignani describes sequences of *Streptococcus pneumoniae* proteins and nucleic acids that could be used for vaccination purposes, Masignani fails to specifically disclose or suggest an isolated detoxified pneumococcal neuraminidase sequence, much less, an isolated detoxified pneumococcal neuraminidase that maintains antigenicity or immunogenicity. Further, Masignani fails to disclose or suggest methods of making and using isolated detoxified pneumococcal neuraminidases. In contrast, as stated above, the present application provides isolated detoxified neuraminidases or antigenic portions thereof and methods for making and using isolated detoxified pneumococcal neuraminidases at least at pages 15-19 of the specification. Further, the present application provides compositions comprising isolated detoxified pneumococcal neuraminidases or antigenic portions thereof at least at pages 8-12 of the specification. Masignani fails to disclose or suggest an isolated detoxified neuraminidase or an antigenic fragment thereof, as recited by claim 1 or each specific modification of a detoxified pneumococcal neuraminidase or antigenic fragment thereof recited in claims 2-17. Additionally, Masignani fails to disclose or suggest compositions comprising detoxified pneumococcal neuraminidases as recited in claims 18-19, 38, and 42. Thus, the cited reference fails to disclose or suggest each and every element of the claims, and claims 1-19, 38, and 42 are novel. Applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 103(a)

The Examiner rejected claims 1-19 and 38-45 under 35 U.S.C. § 103(a) for allegedly being obvious based on Masignani in view of U.S. Patent No. 7,202,056 ("Lee"). Applicants respectfully traverse this rejection.

The Examiner, at page 9, lines 7-10, of the Office Action, stated, "it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have taken the immunogenic polypeptides disclosed by Masignani et al and create compositions for administration via nasal spray or nebulizer as taught by Lee et al." As stated above, Masignani fails to disclose or suggest an isolated detoxified pneumococcal neuraminidase or antigenic fragment thereof, a method of making an isolated detoxified pneumococcal neuraminidase or antigenic fragment thereof, a method of using an isolated detoxified pneumococcal neuraminidase or antigenic fragment thereof, and compositions comprising an isolated detoxified pneumococcal neuraminidase or antigenic fragment thereof. Lee fails to make up for the deficiencies of Masignani, as Lee also fails to disclose or suggest an isolated detoxified pneumococcal neuraminidase, compositions comprising an isolated detoxified pneumococcal neuraminidase, methods of making and using an isolated detoxified pneumococcal neuraminidase. Therefore, the cited references, in combination, fail to disclose or suggest each and every element of the claims.

Further, the detoxified pneumococcal neuraminidases claimed in the present application have surprising and unexpected properties. The specification at page 2, lines 4-11, states that the major reservoir or pneumococci resides in the human nasal carriage and that any medical intervention that prevented colonization of the nasal carriage would not only eliminate the risk of disease in treated individuals but would also result in lowering the risk of infection of untreated members of the community. As described in the specification at page 45, lines 5-16, pneumococci NanA mutants were recovered from tissues, including olfcactory bulbs and CNS tissues in far fewer numbers than wildtype pneumococci. These findings demonstrate that nasal carriage is a prerequisite for more invasive disease and that "interventions capable of reducing carriage, *such as immunization with NanA*, will offer protection against pneumonia, meningitis, otitis-media, and sepsis." See page 45, lines 14-16 of the specification. Moreover, in the enclosed abstract by Dr. James Watt, Dr. Fredrik van Ginkel, and Dr. David Briles, inventors of the present application, presented at the 6th International Symposium on Pneumococci and Pneumococcal Diseases, June 8-12, 2008, it is stated that "NanA-mediated immune protection against colonization does not require an enzymatically active neuraminidase." Therefore, there

is a technical advantage to using the detoxified pneumococcal neuraminidase to provide immune protection as described in Example 2 of the specification. As such, the detoxified pneumococcal neuraminidase of the present application possesses surprising and unexpected properties not deducible from Masignani, especially since Masignani fails to disclose or suggest a detoxified pneumococcal neuraminidase or any properties of a detoxified pneumococcal neuraminidase. As Lee fails to disclose or suggest a detoxified pneumococcal neuraminidase, Lee fails to make up for the deficiencies of Masignani.

Therefore, claims 1-19 and 38-45 are not obvious based on Masignani in view of Lee at least because Masignani and Lee fail to disclose or suggest each and every element of the claims. Further, the claims of the present application provide detoxified pneumococcal neuraminidases with surprising and unexpected properties. As such, claims 1-19 and 38-45 are not obvious based on Masignani in view of Lee. Applicants respectfully request reconsideration and withdrawal of this rejection.

It is believed that all issues raised by the Examiner have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

It is believed that no fee is due. However, please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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Tiffany B. Salmon, Ph.D.
Reg. No. 55,589

1180 Peachtree Street, N.E., 21st Floor
Atlanta, GA 30309
Telephone: (404) 892-5005
Facsimile: (877) 769-7945

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